Chapter

Polyunsaturated Fatty Acid Metabolism in the Brain and Brain Cells

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Abstract

Dietary polyunsaturated fatty acids (PUFAs) have gained more importance these last decades since they regulate the level of long-chain PUFAs (LC-PUFAs) in all cells and especially in brain cells. Because LC-PUFAs, especially those of the n-3 family, display both anti-inflammatory and pro-resolution properties, they play an essential role in neuroinflammation. Neuroinflammation is a hallmark of neurological disorders and requires to be tightly controlled or at least limited otherwise it can have functional consequences and negatively impact the quality of life and well-being of patients. LC-PUFAs exert these beneficial properties in part through the synthesis of specialized pro-resolving mediators (SPMs) that are involved in the resolution of inflammation and to the return of homeostasis. SPMs are promising relevant candidates to resolve brain inflammation and to contribute to neuroprotective functions and lead to novel therapeutics for brain inflammatory diseases. Here we present an overview of the origin and accumulation of PUFAs in the brain and brain cells and their conversion into SPMs that are involved in neuroinflammation and how nutrition induces variations in LC-PUFA and SPM levels in the brain and in brain cells.

Keywords: long-chain polyunsaturated fatty acids (LC-PUFAs), docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), specialized pro-resolving mediators (SPMs), nutrition, neuroinflammation, brain, brain cells

1. Introduction

Polyunsaturated fatty acids (PUFA) are essential fatty acids including precursors and long-chain PUFAs (LC-PUFAs). Precursors have to be provided by the diet because they cannot be produced by mammals [1]. They can be converted into LC-PUFAs. However, as the conversion rate is very low in human [2, 3], it is recommended to consume also LC-PUFAs that modulate LC-PUFA composition of brain and brain cells. Altered dietary intake and/or PUFA metabolism has been reported to be involved in a number of neurological disorders *via* sustained neuroinflammatory processes [4]. Indeed, LC-PUFAs are key regulators of inflammation [5]. LC-PUFAs can be metabolized into specific derivatives such as specialized pro-resolving mediators (SPMs) that have anti-inflammatory and pro-resolving properties [6–9], giving the LC-PUFAs and their biological derivatives a growing interest to treat inflammation and more specifically neuroinflammation. Hence, they may

represent a relevant alternative or complementary strategy to treat pathologies involving neuroinflammation. Here, we will review the literature on PUFAs and their bioactive lipid derivatives in the brain and brain cells. The book chapter will be divided in two main sections: in the first one, we will report data on the origin of PUFAs in the brain and on PUFA content in brain and brain cells and in the second one, we will review recent data on the bioactive lipid derivatives and their role in neuroinflammation. We will discuss how nutrition, an environmental factor to which individuals are exposed throughout their life, is a factor of variation of PUFA and their mediator contents in both sections. We will focus on total brain but also on brain cells since brain cells are differently affected by dietary supply.

2. PUFAs in the brain and brain cells

2.1 Origin of PUFAs in the brain

2.1.1 Metabolism of PUFAs

PUFAs are fatty acids containing more than one double bond on their carbon chain. They are classified into two main series, the n-6 PUFAs and the n-3 PUFAs depending on the position of the first double bond from the methyl terminal end. N-6 PUFAs have the first double bond at the 6th carbon and n-3 PUFAs at the 3rd. Of these two series, linoleic acid (LA) and alpha-linolenic acid (ALA) are the precursors and are essential fatty acids because mammals cannot synthesize them. *In vivo*, these precursors can be elongated, desaturated and beta-oxidized into fatty acids with additional double bonds and carbon atoms leading to long-chain PUFAs (LC-PUFAs, ≥20 carbon atoms) (**Figure 1**). This metabolic pathway requires specific Δ6 and Δ5 desaturases and elongases that are common to both n-6 and n-3 PUFAs, meaning that these pathways are in competition [10]. LC-PUFA

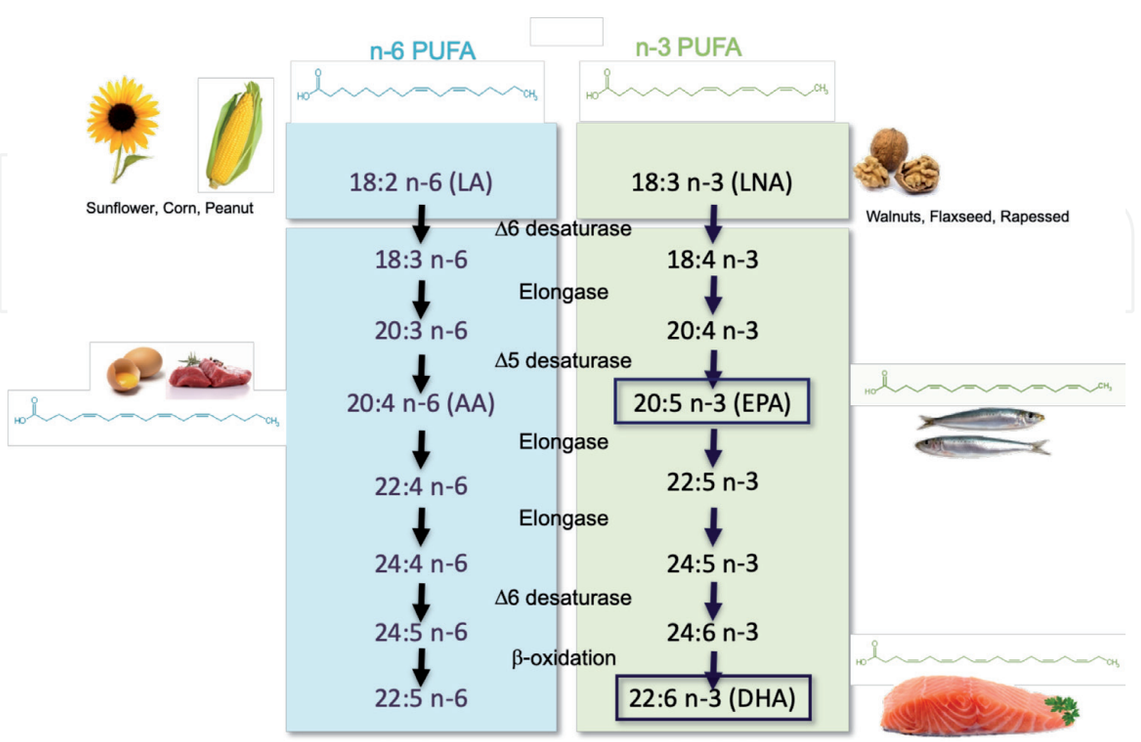

Figure 1.
Synthesis pathways of n-6 and n-3 LC-PUFA and main dietary sources of PUFAs. LA: linoleic acid; LNA: linolenic acid; AA: arachidonic acid; EPA: eicosapentaenoic acid; DHA: docosahexaenoic acid.

biosynthesis takes place mainly in the liver, especially in both microsomes and peroxisomes [11]. However, the brain also possesses the enzymatic equipment and can synthesize LC-PUFAs. The main LC-PUFAs for the n-6 and n-3 series, due to their role as precursors of bioactive derivatives and due to their level in the brain, are arachidonic acid (AA, 20:4 n-6) and docosahexaenoic acid (DHA, 22:6 n-3) [12, 13]. Eicosapentaenoic acid (EPA, 20:5 n-3) is also an important n-3 LC-PUFA as it is also a precursor of bioactive derivatives despite its low level in the brain because of its rapid β-oxidation [14]. Docosapentaenoic acid (DPA, 22:5 n-6) for the n-6 family is also relevant because it replaces DHA in the membranes in case of dietary n-3 PUFA deficiency. LC-PUFAs are mainly esterified in phospholipids. They are also present as free LC-PUFA in very low amount: 1 nmole/g tissue *versus* 10 μmoles/g [15].

2.1.2 Dietary origin

The precursors LA and ALA are found mainly in vegetables, oils, and seeds (60% of LA in sunflower oil and 10% of ALA in rapeseed oil, for example) (**Figure 1**) [16, 17]. Although human can synthesize LC-PUFAs from these precursors, the conversion efficiency is very low (<5%) even in healthy adults [2, 3]. Hence, the main part of LC-PUFAs comes from the diet. AA is found in meats (5–10%) and eggs (15%) [18, 19] and DHA and EPA are found in fatty fishes (18.7% EPA + DHA in salmon, 32.9% EPA + DHA in tuna, for example) (**Figure 1**) [20]. However, lean fishes (sole, codfish, etc.) contain also appreciable amounts of DHA and EPA. Therefore, LC-PUFAs dietary intakes are crucial to maintain adequate levels of LC-PUFAs in membranes. That is why there are dietary recommendations for PUFAs. Dietary intakes recommend ~500 mg/day in EPA and DHA (2 portions of fish/week) and a ratio LA/ALA close to 4–5 to meet all the needs of the body into DHA and to protect against cardiovascular disease risk [21, 22]. Preclinical and clinical studies indicate that increasing dietary ALA and reducing LA are beneficial in increasing n-3 LC-PUFA bioavailability [23, 24]. Despite these recommendations, dietary n-3 PUFA intake is insufficient, both for the precursor ALA and the LC-PUFAs DHA and EPA. Indeed, in the western diet, there is an imbalance between n-6 and n-3 PUFAs leading to an n-3 PUFA consumption 12–20 times lower than n-6 PUFA consumption [10, 25]. This is due to the increased industrialization in the developed nations accompanied by changes in dietary habits. It is particularly characterized by an increase in LA and AA together with a decrease in ALA and DHA. A high intake of LA associated with a low intake of ALA leads to the accumulation of n-6 PUFAs, including AA. In case of severe n-3 PUFA deficiency, the expression of desaturases and elongases are upregulated in the liver in order to compensate and provide DHA to the brain [26, 27]. In addition, under dietary n-3 PUFA deficiency, the half-life of brain DHA is increased by twofold as under balanced diet [28]. Dietary lipids, representing 35–40% of total energy intake, are essentially found (90–95%) in the form of triglycerides (a glycerol backbone with three fatty acids). They are also found in the form of phospholipids (in which the 3-position on the glycerol is replaced by a phosphorylated alcohol function). There is still a debate concerning the better form to enhance EPA/DHA bioavailability, krill oil as a source of phospholipids or fish oil as a source of triglycerides [29, 30]. More studies have to be performed.

2.2 PUFA content in the brain

The brain contains high levels of PUFAs (25–30%) that are mainly DHA (n-3 PUFA) (12–14% of total fatty acids) and AA (n-6 PUFA) (8–10% of total fatty acids) [12, 31–35]. Most LC-PUFAs accumulate during brain development, especially

during the perinatal period: in humans between the beginning of the third trimester of gestation and 2 years and in rodents between the 7th and the 21st postnatal day [36–38]. These periods correspond to the rapid neuronal maturation, synaptogenesis, and gray matter expansion [39, 40]. The brain LC-PUFA content differs in brain structures [12, 31, 35, 41, 42], for example, in the adult C57Bl6/J mice, AA is higher in hippocampus (10.2%), followed by the prefrontal cortex (9.7%), the hypothalamus (8.5%), the cortex (7.7%), the cerebellum (6.5%), and the brain stem (5.5%) [12]. DHA is higher in the prefrontal cortex (14.3%) and in the hippocampus (13.7%), followed by cerebellum (12.2%) and cortex (11.9%), hypothalamus (10.1%), and brain stem (8.2%) [12]. Then the AA/DHA ratio varies from 0.75 to 0.85 in the hypothalamus and hippocampus to 0.54 in the cerebellum. These variations may be due to different LC-PUFA entry mechanisms into the brain or to different incorporation into membranes of cells composing the structure considered. These levels are comparable in human: prefrontal cortex contains between 12.3 and 15.9% of DHA in rats and mice and between 14.1 and 15.9% [12, 35, 43, 44].

2.3 PUFA content in brain cells

Brain cells comprise neurons and glial cells: 70% astrocytes, 10–15% oligodendrocytes, and 10–15% microglial cells [45]. Very few studies reported the fatty acid composition of the individual cells. Bourre et al. determined the fatty acid composition in neurons, astrocytes, and oligodendrocytes in 15- or 60-days rats and confirmed previous results obtained in 1973 and 1981 [46–49]. We recently described the fatty acid composition of microglial cells in 21-days mice [46, 50].

Neurons cannot synthesize LC-PUFAs but can incorporate them in their membranes. They contain 8.2–8.3% DHA and 2.2–2.8% n-3 DPA (22:5 n-3) for n-3 LC-PUFAs, 10.3–15.1% AA, 2.2% n-6 DPA, and 1.0–2.1% adrenic acid (22: 4 n-6) for n-6 LC-PUFAs [46]. They contain 3.1–6.9% LA. Then the ratio n-3/n-6 is 0.46–0.50.

Astrocytes are supportive glial cells that play many roles including synaptic transmission and energy metabolite furniture to different neural elements. They respond to all forms of central nervous system (CNS) insults through a process referred to as reactive astrogliosis. Dysfunctions of astrocytes result in pathological changes in the CNS. Astrocytes contain 10.6–12.1% DHA and 0.7–1.3% of n-3 DPA for n-3 LC-PUFAs and 10.1–10.3% of AA, 2.5–2.7% of n-6 DPA and 2.4–2.7% adrenic acid (22:4 n-6) [46]. They contain few PUFA precursors: only 1.2–1.4% of LA and no ALA. The ratio n-3/n-6 is 0.72–0.76.

Oligodendrocytes provide a supporting role for neurons and are involved in the formation of myelin sheaths of nerve cell axons. They are highly dynamic and can respond to environmental influences and neuronal activity. They can also regenerate myelin spontaneously after CNS injury. Any disturbances in their functioning are associated with major diseases of the nervous system. They contain mainly 5.1% DHA for n-3 LC-PUFAs and 9.3% AA and 3.5% n-6 DPA for n-6 LC-PUFAs [46]. They contain not as much as LA: only 2.7%. The ratio n-3/n-6 is 0.33.

Microglial cells are the innate immune cells of the brain. They play a major role in synaptogenesis, synapse structure and function, and neuroinflammation. They perpetually scan and control their environment and once activated, they deliver pro-inflammatory and pro-regeneration responses. Their fatty acid composition differs from that of the other brain cells. In all these cells, DHA is the main fatty acid. Microglial cells are characterized by few DHA (<1%) and n-3 DPA (0.1%) but high content of EPA (3.7%) [50]. They contain few AA (1.6%). They contain PUFA precursors: 8.0% LA and 1.3% ALA. The ratio n-3/n-6 is 0.42. This microglial fatty acid composition also differs from the whole brain hippocampus that contains higher DHA than EPA [51]. Then, it seems that EPA metabolism is different in microglial cells than in other brain cells and the

whole brain structure. It is not highly β-oxidized as in the whole brain [52]. More studies have to be performed to elucidate the role of EPA in microglial cells.

2.4 Nutrition as a major factor of variation of brain and brain cell PUFA content

Nutrition is an environmental factor to which individuals are continuously exposed throughout life. And it is an environmental factor that changed a lot these last decades. Indeed, there was a dramatic reduction in the dietary supply of n-3 PUFAs in western societies associated with a drastic increase in the n-6 PUFAs, leading to an imbalanced n-6/n-3 PUFA ratio estimated at 12–20 in developed countries instead of five recommended [10].

This is particularly important considering that brain fatty acid composition varies with the fatty acids of the dietary supply [53]. Indeed, PUFA content is strongly impacted by the dietary PUFAs in all brain structures [12, 54]. A diet deficient in n-3 PUFA precursor during development and/or adulthood decreases brain DHA in all brain structures; the prefrontal cortex and the hippocampus that contain the highest DHA content are the most sensitive whereas the hypothalamus that contains the lowest DHA, is the least sensitive [12, 31, 55–58]. These differences may be attributed to the evolution of brain performance [59, 60]. In such case of n-3 PUFA deficiency, changes in metabolism occur: the half-life of DHA increases in the brain to reduce its loss [61] and the activity of DHA synthesis enzymes (Δ6 destaurase and elongase) is increased in the liver [26, 62, 63]. In contrast to the deficiency, the supplementation in n-3 LC-PUFAs increases brain DHA [64–67]. DHA supplementation is more efficient than ALA supplementation to increase brain DHA [68, 69]. A DHA supplementation is also efficient to reverse brain DHA decrease due to an n-3 PUFA deficiency or to aging [33, 70–72]. Also, genetic models of n-3 PUFA enrichment such as Fat-1 mice possess higher brain DHA content [12, 73–77].

Brain cells are also impacted by dietary PUFA supply. An n-3 PUFA precursor-deficient diet decreases DHA in neurons (4.6% *versus* 8.2% in 15-day old animals and 2.4 *versus* 8.3% in 60-day old animals), astrocytes (3.1 *versus* 10.6% in 15-day old animals and 5.7 *versus* 12.1% in 60-day old animals), and oligodendrocytes (0.1% *versus* 5.1% in 60-day old animals) [46]. These changes decrease the n-3/n-6 ratio (0.24 *versus* 0.46–0.50 in neurons, 0.12–0.25 *versus* 0.72–0.76 in astrocytes and 0.02 *versus* 0.33 in oligodendrocytes). Interestingly, we recently find that a maternal n-3 PUFA precursor deficiency increases n-6 DPA but does not affect DHA level in microglial cells in 21-day-old animals, suggesting that these cells are protected from n-3 PUFA deficiency [50]. However, we also report that a maternal n-3 LC-PUFA supplementation increases DHA levels and decreases n-6 DPA levels in these animals, confirming results previously obtained in glial cells [78, 79].

All these results suggest that brain DHA levels are highly variables, depending on the brain structures or brain cells considered and on the dietary fatty acid intake. This may have consequences on inflammatory processes since n-3 LC-PUFAs have immunomodulatory properties [80].

3. Bioactive PUFA derivatives

3.1 Bioactive PUFA derivative metabolism

3.1.1 PUFA derivative synthesis pathways

Some of the immunomodulatory properties of LC-PUFAs are attributed to the synthesis of bioactive lipid mediators. Different lipid mediators are synthesized: those

involved in the regulation of inflammation such as the eicosanoids (prostaglandins, leukotrienes, and thromboxanes) and those implicated in the resolution of inflammation called specialized pro-resolving mediators (SPMs, resolvins, protectins, and maresins) (**Figure 2**). Among the eicosanoids, those synthesized from n-3 PUFAs are less potent inflammatory than those synthesized from n-6 PUFAs [81] highlighting the interest to increase n-3 PUFA and decrease n-6 PUFA contents in the membranes. Then, when co-present, EPA-derived eicosanoids antagonize those synthesized from AA. The main EPA-derived mediators include 3-series prostaglandin (PG), 5-series leukotriene (LT), and 3-series thromboxane (TX), reported to be nonactive (**Figure 2**). DHA is also converted into 3-series PG (**Figure 2**). In addition, eicosanoids synthesized from AA and EPA act in competition as they share the same G-protein-coupled receptors. Moreover, EPA is a competitive inhibitor to AA. Indeed, it reduces the production of AA by inhibiting the activity of Δ5 desaturase converting dihomo-gamma-linolenic acid (dGLA) into AA [81]. EPA also reduces *in vitro* the production of AA-derived eicosanoids by inhibiting the activity of cyclooxygenase-2 (COX-2) and 5-lipoxygenase (5-LOX) generating the eicosanoids [82–84]. Eicosanoids are synthesized first in the time course of the inflammatory response. Then, there is a switch in the bioactive lipid mediator class: SPMs derived from n-3 LC-PUFAs are synthesized to induce the resolution of inflammation and a return to homeostasis (**Figure 3**). DHA is the precursor of D-series resolvins, neuroprotectin D1 (NPD1), and Maresin 1–2 (Mar1–2) and EPA is the precursor of E-series resolvins, all these derivatives underlying most of the beneficial effects attributed to their precursors [1, 85–87]. These derivatives have both anti-inflammatory and pro-resolution properties without immune suppression [6, 8, 88, 89]. SPMs actively orchestrate and finely tune the inflammatory response. They decrease pro-inflammatory cytokines and increase anti-inflammatory cytokines and accelerate the phagocytosis of cellular debris and dead cells without immune suppression. They are synthesized *via* COX-2, LOX, and cytochrome P450 monooxygenases (CYP450) once they have been released from membrane phospholipids by phospholipase A2 in response to stimulation. These

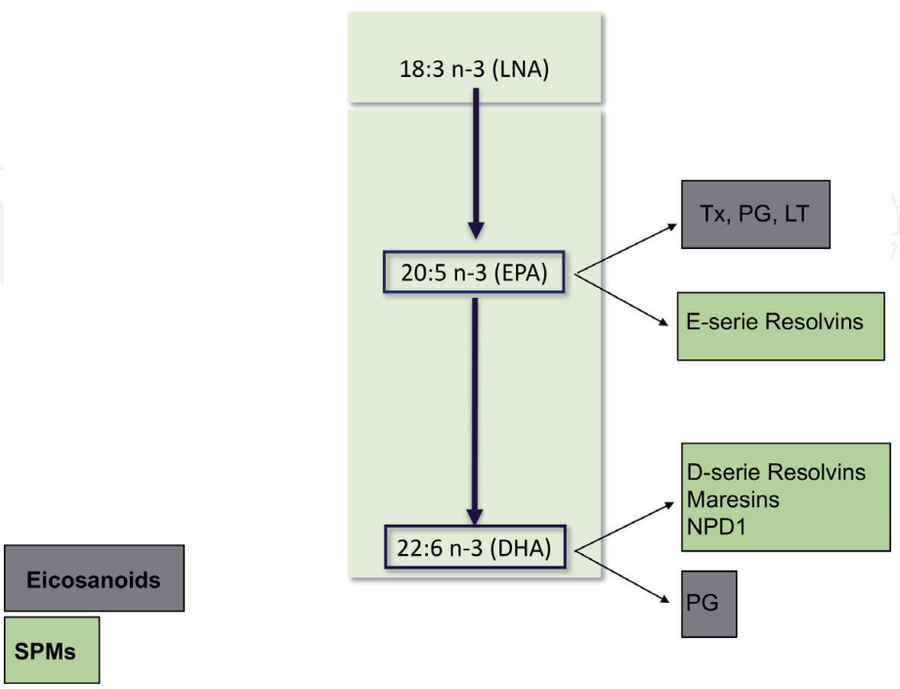

Figure 2.
Main bioactive lipid mediators synthesized from n-3 PUFAs. DHA: docosahexaenoic acid; EPA: eicosapentaenoic acid; LNA: linolenic acid; LT: leukotriene; NPD1: neuroprotection D1; PG: prostaglandin; SPMs: specialized pro-resolving mediators; Tx: thromboxane.

enzymes are expressed in the brain [90–92]. In response to lipopolysaccharide (LPS) that induces inflammation, COX-2 is rapidly expressed in the hippocampus [69, 93] and inhibition of COX-2 delays resolution of acute inflammation [94]. 15-LOX and 5-LOX are the most abundant LOX in the brain [90]. 15-LOX has a dual role since it is involved in neurodegeneration and neurotoxicity due to the increased stress it generates [95–97] and is also involved in neuroprotection [98]. 15-LOX deletion or inhibition decreases SPM production in the brain and cognitive alterations [90]. CYP450 generates n-6 derived epoxides that are anti-inflammatory [99–102]. These enzymes are also expressed in microglia, astrocytes, oligodendrocytes, and neurons [103–106].

3.1.2 Bioactive lipid mediators

DHA is converted into monohydroxy DHA (17-HDHA) by acetylated COX-2, CYP450, and 15-LOX [107, 108] and then into RvD1 by 5-LOX [109, 110]. RvD1 and its precursors have mostly been described at the periphery but have also been detected in the brain. RvD1 was measured in mouse brain following cerebral ischemia. Its level is increased following a DHA intravenous injection [111] and modulated during inflammation: it decreases at the beginning and then increases during the resolution phase [112]. RvD1 acts through the regulation of microRNAs (miRNAs) that modulate the expression of target genes such as inflammatory genes [113–117]. DHA can also be converted into di-hydroxy-DHA termed protectin D1 (PD1) or neuroprotectin D1 (NPD1) when produced in the CNS by 5- and 15-LOX [118–121]. NPD1 was measured in hippocampus. Its level greatly is increased following brain ischemia or acute central LPS injection [70, 122] and decreased in the hippocampus of Alzheimer's disease patients [123]. NPD1 acts through NFkB and then decreases pro-inflammatory gene expression [122, 124, 125]. At last, DHA can also be converted into 14-HDHA and then in Mar1–2 by 12/15-LOX [107, 108, 126]. Mar1 and its precursor 14-HDHA have recently been identified in the hippocampus of mice [70]. Its level is decreased in post-mortem Alzheimer's disease patients contributing to the progression of this pathology [127]. Mar1 promotes the resolution of inflammation, reducing pro-inflammatory cytokines, silencing pro-inflammatory signaling cascades, and enhancing M2 repair macrophage phenotype after cerebral ischemia or spinal cord injury [128–130] (**Figure 3**).

EPA is converted into resolvins E1, E2, and E3 by acetylated COX-2 or CYP450 *via* 18R-HEPE by 5- or 15-LOX [107, 131, 132]. RvE1 and its precursor have been detected in hippocampus [70, 133, 134]. RvE1 inhibits NFκB signaling pathway and then decreases LPS-induced proinflammatory cytokines (TNF-α, IL-6, and IL-1β) gene expression in microglial cells [117].

3.1.3 SPM receptors

SPMs act through specific receptors, some but not all of them have recently been identified. RvD1 acts through lipoxin A4 receptor/formyl peptide receptor 2 (ALX/Fpr2) in rodents and G protein coupling receptor 32 (GPR32) in human [109] at picomolar range but induces biological effects at nanomolar range [110, 135]. RvE1 directly binds to its receptor G protein coupling receptor ChemR23 or chemokine like receptor 1 (CMKLR1) [131]. It is also a partial agonist of a leukotriene B4 receptor (BLT1) [136]. In the CNS, ALX/Fpr2 has been identified in the brainstem, spinal cord, hypothalamus, cortex, hippocampus, cerebellum, and striatum [137] and ChemR23 in the prefrontal cortex, hippocampus, and brainstem [138]. At the cellular levels, these two receptors have been detected in microglial cells [117, 139], neurons [137, 140] and astrocytes [96, 113] (**Figure 3**).

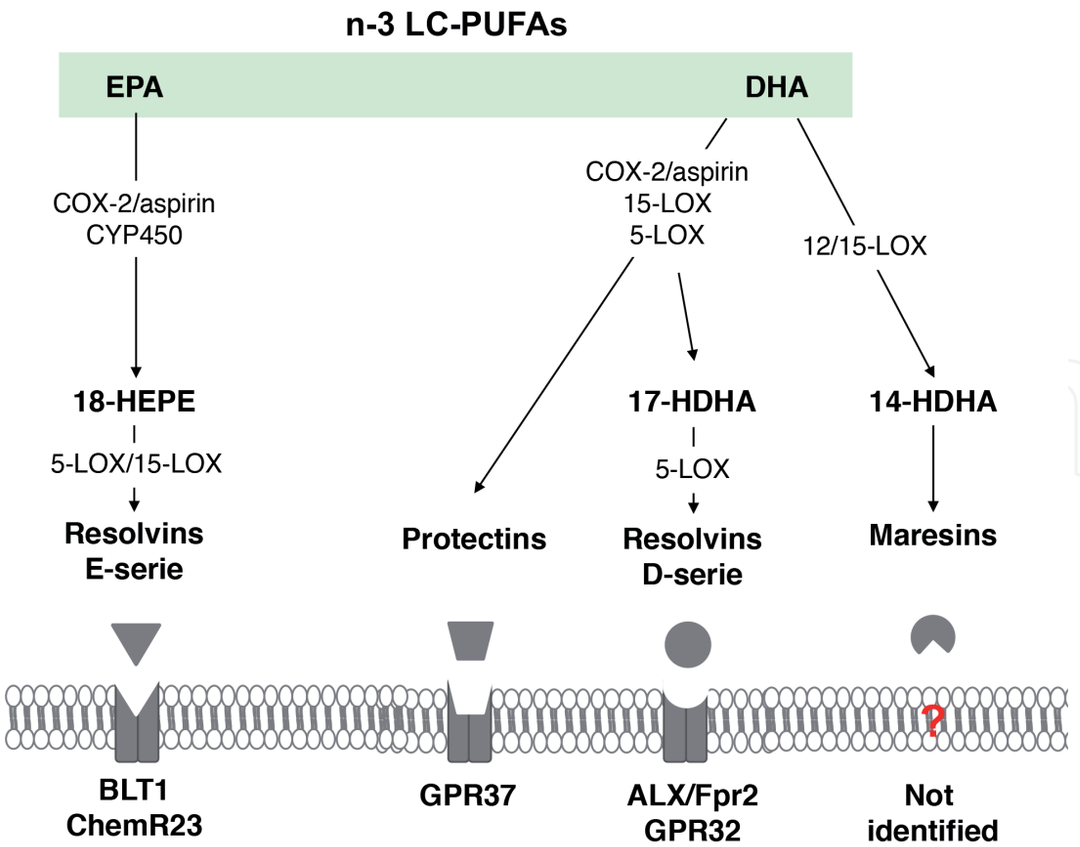

Figure 3.
Specialized pro-resolving mediator (SPM) synthesis. 14-HDHA: 14-hydroxy-docosahexaenoic acid; 17-HDHA: 17-hydroxy-docosahexaenoic acid; 18-HEPE: 18-hydroxy-eicosapentaenoic acid; ALX/Fpr2: N-formyl peptide receptor 2; BLT1: leukotriene B4 receptor; COX-2: cyclooxygenases; DHA: docosahexaenoic acid; EPA: eicosapentaenoic acid; GPR32/37: G protein-coupled receptor 32/37; LC-PUFAs: long chain polyunsaturated fatty acids; LOX: lipoxygenases.

Other receptors have not been identified yet (Mar1 receptor) [127] or identified only at the periphery in macrophages but not in microglia (NPD1 receptor) [141].

In the next sections, we will focus on the role of these SPMs to better understand the beneficial effects of the n-3 PUFAs.

3.2 Role of bioactive lipid derivatives in neuroinflammation

SPMs have multiple biological roles, focusing to the return to homeostasis. In human serum, DHA- and EPA-derivatives represent 30.7 and 25.9% of the identified SPMs, respectively [142, 143]. The most SPMs studied are RvD1 and RvE1 because they have powerful anti-inflammatory and pro-resolution properties. We will then detail the biological roles for these two bioactive mediators.

3.2.1 Biological role of RvD1 and RvE1 in humans

The effect of RvD1 was mainly studied in patients suffering from Alzheimer's disease. Interestingly, RvD1 levels in cerebrospinal fluid are positively correlated with the enhancement of cognitive functions of patients with dementia [96]. Moreover, it was suggested *in vitro* in macrophages isolated from Alzheimer's patients that RvD1 may be involved in Aβ phagocytosis [144, 145]. Then the decrease in RvD1 levels in Alzheimer's patient brain could contribute to the disease development. To our knowledge, the effect of RvE1 in humans was shown at the periphery (on patients undergoing hepatobiliary resection, pulmonary

inflammation, and bone disease periodontitis) [146–148] but not at the brain level on patients suffering from neurodegenerative diseases.

3.2.2 Biological roles of RvD1 and RvE1 in rodents

RvD1 and RvE1 are active in reducing the pro-inflammatory status in the CNS. Indeed, the precursors of RvD1, 17R-HDHA, and 17S-HDHA decrease the production of pro-inflammatory cytokines TNF-α in the spinal cord and IL-1β and TNF-α in the hippocampus [70, 149]. Moreover, RvD1 is able to induce the polarization of macrophages and microglia toward an M2 phagocytic phenotype [150–152]. In addition, RvD1 reduces neuroinflammation *via* miRNA in a model of remote damage [113]. RvE1 also modulates inflammation by reducing the proinflammatory cytokines IL-1β and IL-6 in the prefrontal cortex and decreases the measures of Aβ pathology in a murine model of Alzheimer's disease [153]. Furthermore, RvE1 treatment decreases brain microglial activation following traumatic brain injury or peripheral brain injury, decreasing the proportion of activated microglia at the expense of ramified microglia [154, 155].

RvD1 is also involved in the prevention of cognitive deficits. In a systemic inflammation model, cognitive decline is prevented by an intraperitoneal (ip) injection of the precursor of RvD1, 17R-HDHA, and is associated with the restoration of transmission and synaptic plasticity and to the prevention of astrogliosis [154, 156]. Moreover, in a model of traumatic brain injury, cognitive deficits are also prevented by an ip chronic administration of 17R-HDHA [154]. Of note, Fat-1 mice that have more brain n-3 LC-PUFAs have higher hippocampus RvD1 that is associated with less cognitive deficits, a better neuronal survival, a decrease in astrocyte and microglial activation and a reduction in pro-inflammatory status following brain ischemia [77, 157]. Inversely, an inhibition of 15-LOX associated with a decrease in RvD1 induces alterations in synaptic plasticity and working memory [90].

Additionally, RvD and E are also associated with the prevention of depressive-like behaviors [158]. An intracerebroventricular (icv) injection of RvD1, D2, E1, E2, or E3 significantly decreases LPS-induced depressive-like behaviors [159–161]. Moreover, an intrathecal injection of 17R-HDHA prevents the occurrence of depressive-like behaviors and is associated with the decrease of pain perception and a restoration of dopamine and glutamate levels in the brain [149, 162]. RvD1 and D2 have also positive effects in chronic mild stress-induced depression and in post-myocardial infarct depression [163, 164].

3.2.3 Biological roles of RvD1 and RvE1 in in vitro brain cell models

The effects of RvD1 were tested on different brain cells. In microglial cells, RvD1 potentiates the activation of the anti-inflammatory M2 phenotype of microglia, enhancing the effect of the anti-inflammatory cytokine IL-4, Arg1, and Ym1 expression and decreasing CD11b expression [152, 155, 165]. Moreover, we showed that RvD1 decreases LPS-induced proinflammatory cytokine (TNF-α, IL-6 and IL-1β) gene expression in microglial BV2 cells *via* the modulation of miRNAs [117]. RvD2 inhibits LPS-induced activation of toll-like receptor 4 (TLR4, the receptor of LPS) and its downstream signaling pathway NFκB [166]. RvE1 plays also a direct role in microglial cells by inhibiting microglial activation and pro-inflammatory cytokine release [117, 155]. These results suggest the pro-resolution activity of RvD1 and RvE1 in microglia. In astrocytes, RvD1 decreases TNF-α release induced by LPS injection [149]. In neurons from spinal nods, RvD1 increases neurite outgrowth [167].

All these studies point out the central role of n-3 LC-PUFA and their bioactive mediators in the regulation of inflammation in the brain, especially through their effect on microglia.

3.3 Nutrition as a factor of variation of SPM levels

The level of these lipid derivatives is modulated by the diet. Indeed, we recently show that a dietary n-3 LC-PUFA supplementation induces an n-3 LC-PUFA enrichment in the hippocampus associated with an increase in n-3 PUFA-derived SPMs and a decrease in n-6 PUFA-derived SPMs [69]. Our results confirm previous ones reporting that oral administration of EPA and DHA results in the generation of EPA-and DHA-derived mediators in the cortex of aged rats [168] and in the down-regulation of the production of n-6 PUFA-derived mediators [169, 170]. The cellular origin of these bioactive lipid derivatives is still unknown. As described in the paragraph above, we know that dietary PUFA supplementation affects PUFA composition in brain cells that potentially could impact brain cell PUFA lipid derivatives. In response to LPS, n-3 LC-PUFA-supplemented mice display an anti-inflammatory SPM profile whereas n-3 LC-PUFA-deficient mice exhibit a pro-inflammatory SPM profile [69]. These results corroborate previous ones *in vivo* [171–176] and *in vitro* in macrophages [177, 178] and microglia [179–181].

The level of SPMs is also dependent on the regulation of their biosynthesis enzymes. 15-LOX mRNA expression increases in n-3 LC-PUFA supplemented group and decreases in n-3 LC-PUFA deficient diet [27, 69, 182]. 15-LOX has beneficial properties such as neuroprotective properties *via* PPAR-γ activation [98] and preservation of cognitive performance through RvD1 formation [90]. 15-LOX has also detrimental effects as it is implicated in neurodegeneration and neurotoxicity through increase of oxidative stress [95–97].

Changes in SPM level and composition induced by the diet can have a great influence on the pro- and anti-inflammatory status of hippocampus and brain cells and reinforce the recommendation of n-3 PUFA-rich diet.

4. Conclusion

These data highlight that n-3 LC-PUFA and their bioactive lipid derivatives are important regulators of neuroinflammation. SPMs are promising therapeutic compounds: they are of natural origin and act in physiologic dose ranges (nanomolar) as compared to EPA and DHA that act at micromolar ranges, and this confers the main advantage to use SPMs. Both brain n-3 LC-PUFA and SPMs are modulated by the diet in the brain and in brain cells confirming the notable role of nutrition in the regulation of inflammation. Alteration in dietary n-3 PUFAs should have dramatic consequences in brain and brain cell PUFA metabolism and finally in the response to neuroinflammation. The use of SPMs to treat neuroinflammation is still in emergence since some data are missing such as the affinity and function of SPM receptors. This field has to be completed. The instability of SPMs may be bypassed by the use of SPM analogues or by their encapsulation. The clinical form and the way of administration should also be defined.

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